Predicting drug bioavailability using PBPK modeling and Global Sensitivity Analysis to identify sensitive parameters

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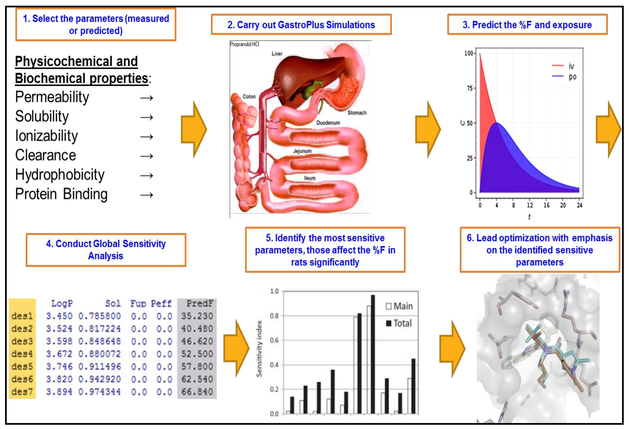
Introduction

- ADME modeling in lead optimization typically includes only QSAR/QSPR predictions of physicochemical properties or simple allometric scaling to predict species variation.
- Many physicochemical properties might be modified to improve exposure. Prioritizing is difficult.
- Physiologically-Based Pharmacokinetic (PBPK) modeling, typically applied on individual compounds for clinical trials, gives more accurate and detailed mechanistic results.
- Inputs required for PBPK modeling are the very same properties, that med chemists intend to modify to improve bioavailability
- Predicting clearance is the challenge in modeling whole series, and that was solved with the help of local QSAR for an apparent intrinsic clearance
- Global Sensitivity Analysis (GSA) of PBPK models for whole chemical series in lead opt. could identify the most effective properties to improve drug exposure.

Approach



Conclusions

- PBPK ADME simulations successfully adapted to lead series:
  - Predicting clearance was solved with a local QSAR for "ideal" CL_{fit}
  - In 3 cases, >80% of %F predictions within 2X all *in silico*
  - Good local QSAR for CL_{fit} with only 15-20 *in vivo* %F's
- Global Sensitivity Analysis finds key properties:
  - Methods developed for GSA of chemical series
  - Unique advice for each series:
    - DPP4 &HSD1 only CL_{int};
    - Kinase: CL_{int} + logD, Sw and RBP
  - Specific advice for each compound within series

Reliable results using local QSAR for fitted intrinsic clearance

DPP-4 Inhibitors (Merck)

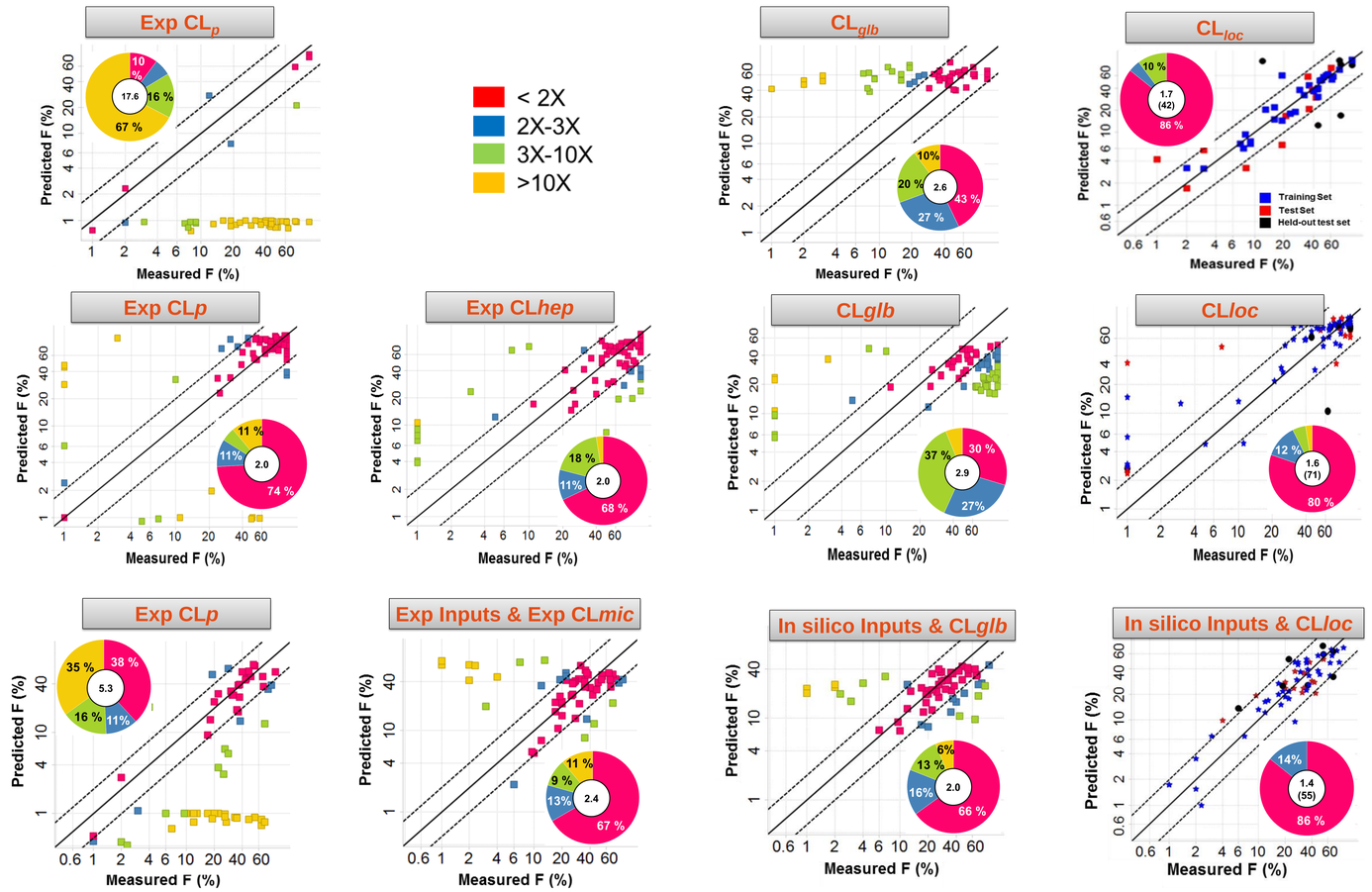
- ✓ 49 Inhibitors
- ✓ RAT *in vivo* data : %F, CLp
- ✓ Physicochem prop & *in vitro* data : --

11β-HSD1 Inhibitors (AZ)

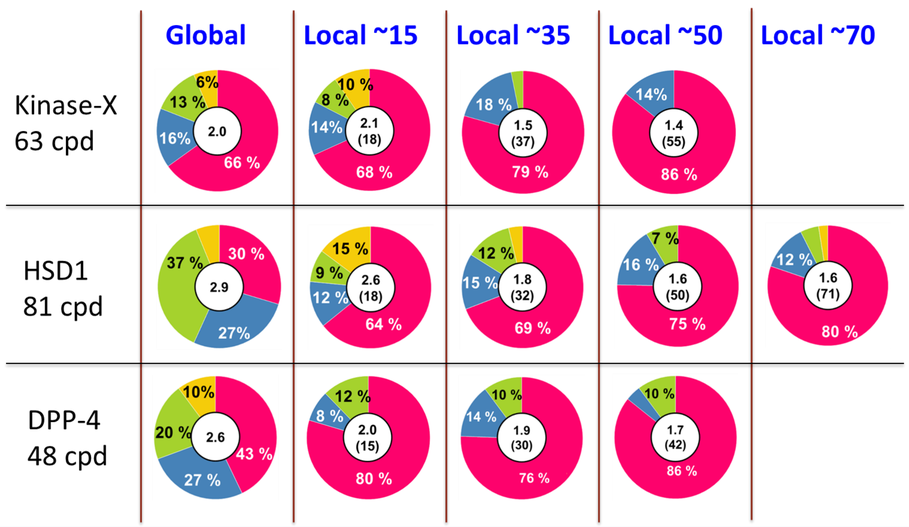
- ✓ 81 Inhibitors
- ✓ RAT *in vivo* data : %F, CLp
- ✓ Physicochem prop & *in vitro* data: $CL_{int(hep)}$

Kinase-X inhibitors (In-House)

- ✓ 63 Compounds
- ✓ RAT *in vivo* data : %F, CLp, AUC, Cmax
- ✓ Physicochem prop & *in vitro* data : Sol, Perm, PPB, $CL_{int(mic)}$



Series can be modeled from as few as 15 rat studies



Sensitivity coefficients identify series-specific properties that control %F